

A Distributed Delay Model for Tuberculosis

Carlos Castillo-Chavez

Biometrics Unit, Cornell University, Ithaca, NY 14853-7801, USA

and

Programa de Investigación en Epidemiología

Departamento de Investigación, Universidad de Belgrano, Buenos Aires, Argentina

Zhilan Feng

Biometrics Unit, Cornell University, Ithaca, NY 14853-7801, USA

and

Angel F. Capurro

Programa de Investigación en Epidemiología

Departamento de Investigación, Universidad de Belgrano

Zabala 1851

1426, Buenos Aires, Argentina

April 20 , 1996

Abstract. One of the typical features of tuberculosis (TB) is that the infectious agent has evolved a symbiotic relationship with the human host; only a relatively small proportion of those who are infected go on to develop the clinical disease. Most people are assumed to mount an effective immune response to the initial infection that limits proliferation of the bacilli, and may lead to long-lasting partial immunity both to further infection and to reactivation of latent bacilli remaining from the original infection. The risk of disease is believed to be at its highest shortly after infection, to decline thereafter, and to increase with age. Often models have divided the routes of progression towards the next stage of a disease by assuming that a fixed proportion of those who become infected—per unit of time—belongs to the ‘slow’ class while the remaining fixed proportion belongs to the ‘fast’ class. This assumption, while appealing, it is restrictive and unnecessary. In this article, we formulate a TB model with a distributed delay in the latent period and look at the effects of long and variable (rather than exponentially distributed) periods of latency on the dynamics of TB.

Key words: Tuberculosis – Distributed Delay–Endogenous Infection–Dynamical Systems–Epidemiology–Communicable Diseases

Introduction

Many mathematical models have been developed to study communicable diseases such as measles, influenza, rubella, and chicken pox (see Hethcote 1976, Dietz 1979, Hethcote, Stech, and van den Driessche 1981, Anderson 1982, Anderson and May 1982, 1991, Dietz and Schenzle 1985, Dietz 1985, Anderson and May 1983, Schenzle 1984, Hethcote and Van Ark 1987, Castillo-Chavez et al. 1988, 1989, Feng 1994, Feng and Thieme 1995). These infectious diseases have several features in common; for example, they cause recurrent epidemic outbreaks, and transmission rates depend strongly on age-dependent contact rates. The etiological agents of these communicable diseases are viruses from different families but all are capable of generating similar epidemiological responses (symptoms) at the level of the individual. Common responses include relatively short latent periods, followed by also relatively short infectious periods and permanent immunity after recovery. It is not completely clear when individuals become infectious (that is, capable of transmitting the disease) as some may become infectious while symptomless. The situation of tuberculosis (TB), despite its fundamental role in the development of bacteriology and modern epidemiology, is different than the situation observed in “childhood” diseases.

A bacterial disease caused by *Mycobacterium tuberculosis*, TB is one of the oldest human diseases. Evidence that supports human cases of TB as well as its role in human mortality exists and goes back for thousands of years (petrified bones from 8,000 B.C.; Hindu texts from 2,000 B.C.; and mummy reliquiae from Egypt and pre-Columbian America, including an Incan child from 700 A.D.). TB or TB-associated symptoms appear to have been the source of inspiration for Frascatorius’ theory of contagion (18th century). However, a search for a cause without a clear understanding of the sources and nature of disease naturally led to what Ayvazian (1993) calls “centuries of nonscientific chaos.” TB was so devastating that it became the dominant force in the development of the fields of bacteriology, modern epidemiology, and public health.

The situation changed when Villeman (19th century) used animal models to establish that TB is a specific infection due to an inoculable agent (Reichman and Hershfield 1993). On March 29, 1882, Robert Koch presented to the Berlin Physiologic Society the results of his research on the causes of disease. Koch’s fundamental research identified the mechanisms for disease transmission and the agents responsible for several diseases, including the etiological agent of TB (Reichman and Hershfield 1993). Koch’s research opened new doors and eventually led to the discovery, by various investigators, of other bacteriological disease agents including the bacilli for typhoid and diphtheria.

Today, with an estimated 8 to 10 million new cases and 3 million deaths yearly (Kochi 1991), TB remains the leading cause of death by an infectious disease. Approximately a third of the world’s population carries *Mycobacterium tuberculosis* (Miller 1993). Dramatic increases in the incidence of TB have also occurred within the United States over

the past few years. From 1985 to 1991, the number of reported cases of TB has increased 18% with 26,283 cases reported in 1991 (Kent 1993). It is predicted that the worldwide situation concerning TB will deteriorate rapidly; during this decade, nearly 90 million new cases will occur and 30 million people will die from TB unless aggressive intervention is undertaken soon (Snider et al. 1994).

The disease is most commonly transmitted from a person suffering from infectious tuberculosis to other persons by infected droplets created when the person with active TB coughs or sneezes. One of the differences between TB and childhood diseases is that the infectious agent has evolved a better symbiotic relationship with the human host, and a relatively small proportion of those infected go on to develop clinical disease (Smith and Moss 1994). Data from a variety of sources suggest that the life-time risk of developing clinically-evident TB after being infected is approximately 10%, with a 90% likelihood of the infection remaining latent (Hopewell 1994). Individuals who have latent infection are not clinically ill or capable of transmitting TB (Miller 1993). As people age, immunity may wane, and the risk of developing active TB as a consequence of either exogenous reinfection (i.e., acquiring a new infection from another infectious individual) or endogenous reactivation of latent bacilli (i.e., reactivation of a preexisting dormant infection) may increase (Styblo 1991, Smith and Moss 1994). The ability of the organism to survive in a latent state and then reactivate many years after the original infection indicates that the tubercle bacillus has enjoyed a long period of coevolution with the human host, a period that has enabled the bacillus to survive in small population groups for long periods of time.

The annual risk of developing tuberculosis in individuals previously infected with *M. tuberculosis* who have survived the initial and higher risk period that follows infection changes with the age of the individual. The following annual risks have been estimated: 1) for children, aged 1- 6, the risk of progression is estimated to be around 0.001648 while for those in the 7-12 age range, the risk is about 0.000770 (Comstock et al. 1974); 2) for adults in the 15-34 age range, the reported risk of progression is between 0.0008-0.0009, while for adults who are over 55 years of age, the risk is reported to be around 0.0010 (Comstock and Edwards 1975). The factors that influence whether or not an infected person will develop tuberculosis must be highly dependent on an individual's immune system. The immune mechanisms of protection against tuberculosis infection are not well known. It is believed that cell-mediated immunity is beneficial but that delayed hypersensitivity is detrimental for the control of TB infection (Dunlap and Briles 1993). The balance between these two related processes must vary among individuals and this balance may be genetically determined (Dunlap and Briles 1993, Sifford and Bates 1991). This balance could be related to the responses of Mononuclear phagocytes (MPs) and T cells to *M. Tuberculosis*. MPs are responsible for killing and/or inhibiting bacterial pathogenesis while T-cells are responsible for the induced immune protection. MPs are the preferred

host cells of *Mycobacterium tuberculosis* while the T-cells seem to enhance pathogen's survival. It is suspected that a coordinated interaction between T-cells and MPs plays a key role in the ability of an individual's immune system to acquire some amount of resistance against tuberculosis—enough to keep the *Mycobacterium tuberculosis* latent for long periods of time. Full protection obviously does not always take place as many individuals remain latently infected and, therefore, likely to develop active TB. It has been proposed that an imbalance in the immune systems—such as the one described above—is behind the 'erratic' activation of clinical disease (Chan and Kaufman 1994).

The effects of concurrent infections, the presence of alternative diseases, or the use of medications that reduce cellular immunity may accelerate TB reactivation. Dutt and Stead (1993) have listed many factors that could facilitate TB reactivation in the elderly. They include: insulin-dependent diabetes, poor nutrition, long-term corticosteroid therapy, other debilitating diseases, smoking, alcohol abuse, and declining cell-mediated immunity. It is known that reactivation of latent tuberculosis is important among HIV-infected (i.e. Selwyn et al. 1991). TB reactivation is also possible in transplant recipients as a result of the use of immunosuppressive agents (Miller et al. 1995). Endogenous reactivation is very common in inner cities like in the Bronx, where 62 % of TB incidence cases have been associated with individuals who have latent TB (Alland et al. 1994). Diabetic persons progress from tuberculin positive status to active tuberculosis more often than non diabetic ones (Boucot et al. 1952, Warwick 1957, Oscarrson and Silwer 1958, Opshal et al. 1961, Henri and Bennett 1985).

Additional evidence related to genetic factors associated with the reactivation of TB endogenous infection has been suggested (Chan and Kaufman 1994). Some studies suggest the possibility of selection playing a role in host resistance in the Qu'appelle Valley Indian Reservation in Canada (Goodman and Motulsky 1979). It is also known that the BCG gene (candidate Nrampl) confers resistance against mycobacteria in mice. BCG acts at the macrophage level and it is thought to control some aspect of macrophage priming for activation (Skamne 1986, Chan and Kaufmann 1994, Brown et al. 1995).

This paper is organized as follows: Section 1 introduces a distributed delay TB model. In Section 2 we compute its basic reproductive number and study its role in the dynamics and stability properties of this model. Section 3 details some of our current efforts and extensions including the incorporation of re-infection and the effects of age-dependent contact rates. An appendix collects some of the mathematical details.

1. A TB model with distributed delay

We divide the host population into the following epidemiological classes or subgroups: susceptibles (S), exposed (E , infected but not infectious), infectious (I , assumed infectious), and effectively treated (T) individuals. N denotes the total population. Our previ-

ous paper (Castillo-Chavez and Feng 1996) introduced a simple model for the transmission of TB:

$$\begin{aligned}\frac{d}{dt}S &= \Lambda - \beta c S \frac{I}{N} - \mu S \\ \frac{d}{dt}E &= \beta c S \frac{I}{N} - (\mu + k)E + \sigma \beta c T \frac{I}{N} \\ \frac{d}{dt}I &= kE - (\mu + r + d)I \\ \frac{d}{dt}T &= rI - \sigma \beta c T \frac{I}{N} - \mu T \\ N &= S + E + I + T.\end{aligned}$$

Λ is the constant recruitment rate, β and $\sigma\beta$ are the average numbers of susceptible and treated individuals infected by one infectious individual per contact per unit of time, $0 \leq \sigma \leq 1$, c is the per-capita contact rate, μ is the per-capita natural death rate, d is the per-capita disease-induced death rate, r is the per-capita treatment rate. We assumed that an individual can be infected only by contacting infectious individuals.

We modify the above model by assuming a variable removal rate (instead of an exponentially distributed latency period) from the E class to the I class. Let $p(s)$ be a function representing the proportion of those individuals exposed at time t and who, if alive, are still infected (but not infectious) at time $t + s$. Assume that

$$p(s) \geq 0, \dot{p}(s) \leq 0, p(0) = 1,$$

and

$$\int_0^\infty p(s)ds < \infty.$$

Then the number of individuals who have been exposed from time 0 to t and are still in class E is given by

$$\int_0^t \beta c [S(s) + \sigma T(s)] \frac{I(s)}{N(s)} p(t-s) e^{-\mu(t-s)} ds,$$

where $-\dot{p}(\tau)$ is the rate of removal of individuals from E class into I class τ units of time after exposed, the number of individuals who become infectious from time 0 to t and are still alive and in I class is

$$(1.1) \quad \int_0^t \int_0^\tau \beta c [S(s) + \sigma T(s)] \frac{I(s)}{N(s)} e^{-\mu(\tau-s)} [-\dot{p}(\tau-s) e^{-(\mu+r+d)(t-\tau)}] ds d\tau.$$

Then we have the following model:

$$\begin{aligned}
(1.2) \quad & \frac{d}{dt}S = \Lambda - \beta cS \frac{I}{N} - \mu S \\
& E(t) = E_0(t) + \int_0^t \beta c[S(s) + \sigma T(s)] \frac{I(s)}{N(s)} p(t-s) e^{-\mu(t-s)} ds \\
& I(t) = \int_0^t \int_0^\tau \beta c[S(s) + \sigma T(s)] \frac{I(s)}{N(s)} e^{-\mu(\tau-s)} [-\dot{p}(\tau-s) e^{-(\mu+r+d)(t-\tau)}] ds d\tau \\
& \quad + I_0 e^{-(\mu+r+d)t} + I_0(t) \\
& \frac{d}{dt}T = rI - \sigma \beta cT \frac{I}{N} - \mu T \\
& N = S + E + I + T,
\end{aligned}$$

where $E_0(t)$ denotes those individuals in E class at time $t = 0$ and still in the latent class, $I_0(t)$ denotes those initially in class E who have moved into class I and are still alive at time t , and $I_0 e^{-(\mu+r+d)t}$ with $I_0 = I(0)$ represents those who are infectious at time 0 and are still alive and in the I class. $E_0(t)$ and $I_0(t)$ are assumed to have compact support (that is they vanish for large enough t).

The I equation in (1.2) is a Volterra integral equation if we change the order of integrations as the following :

$$\int_0^t \int_s^\tau \beta c[S(s) + \sigma T(s)] \frac{I(s)}{N(s)} e^{-\mu(\tau-s)} [-\dot{p}(\tau-s) e^{-(\mu+r+d)(t-\tau)}] d\tau ds,$$

and notice that

$$\begin{aligned}
(1.3) \quad & \int_s^\tau e^{-\mu(\tau-s)} [-\dot{p}(\tau-s) e^{-(\mu+r+d)(t-\tau)}] d\tau \\
& = -e^{-(\mu+r+d)(t-s)} \int_0^{t-s} \dot{p}(u) e^{(r+d)u} du \\
& =: a(t-s).
\end{aligned}$$

Therefore we can rewrite the I equation in (1.2) as

$$(1.4) \quad I(t) = \int_0^t a(t-s) \beta c[S(s) + \sigma T(s)] \frac{I(s)}{N(s)} ds + I_0 e^{-(\mu+r+d)t} + I_0(t).$$

Results on well-posedness found in Miller (1971) guarantee the existence and uniqueness of solutions as well as their continuous dependence on parameters for System (1.2) as a system of nonlinear integral equations.

The positivity of solutions can be proved similarly to Castillo-Chavez et al. (1989).

2. Equilibrium points and their stabilities

In this section we assume that the probability of being infected for a treated individual is the same as for a susceptible individual, i.e., $\sigma = 1$. Let

$$W = S + T, \quad B = \beta c W \frac{I}{N}.$$

Then System (1.2) with the I equation replaced by (1.4) becomes

$$\begin{aligned} \frac{d}{dt}W &= \Lambda - B - \mu W \\ E(t) &= E_0(t) + \int_0^t B(s)p(t-s)e^{-\mu(t-s)}ds \\ I(t) &= I_0e^{-(\mu+r+d)t} + I_0(t) + \int_0^t a(t-s)B(s)ds \\ B(t) &= \beta c W(t) \frac{I(t)}{N(t)}. \end{aligned} \tag{2.1}$$

The basic reproductive number in this case is given by

$$\mathcal{R}_0 = \beta c \int_0^\infty a(\tau)d\tau =: \beta c D_I, \tag{2.2}$$

where

$$D_I = \int_0^\infty a(\tau)d\tau,$$

and $a(u)$ is given by (1.3).

Let

$$D_E = \int_0^\infty p(s)e^{-\mu s}ds,$$

then D_E is the death-adjusted mean length of the latent period. The relation between D_I and D_E is given by

$$D_I = \frac{1}{\mu + r + d}(1 - \mu D_E). \tag{2.3}$$

Remark: in the case of an exponentially distributed latent period with a mean length $1/k$ we have $p(t) = e^{-kt}$, and the formulae (2.2) and (2.3) give

$$\mathcal{R}_0 = \beta c D_I = \left(\frac{\beta c}{\mu + r + d} \right) \left(\frac{k}{k + \mu} \right).$$

System (2.1) with $E_0(t) = I_0(t) = I_0 = 0$ always has the disease-free equilibrium

$$(W_0, E_0, I_0) = \left(\frac{\Lambda}{\mu}, 0, 0 \right),$$

and has no other constant solution. Since $E_0(t)$ and $I_0(t)$ are zero for large t , and $e^{-(\mu+r+d)t} \rightarrow 0$ as $t \rightarrow \infty$, it could be expected that $(\Lambda/\mu, 0, 0)$ is an asymptotic equilibrium of (2.1) as $t \rightarrow \infty$. This is shown by the following theorem.

Theorem 1. *If $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium $(\frac{\Lambda}{\mu}, 0, 0)$ of the system (2.1) is a global attractor, i.e., $\lim_{t \rightarrow \infty} (W(t), E(t), I(t)) \rightarrow (\frac{\Lambda}{\mu}, 0, 0)$ for any positive solutions of the system (2.1).*

The proof can be found in Appendix A.

The following result shows that when $\mathcal{R}_0 > 1$, the disease will persist in the population.

Theorem 2. *If $\mathcal{R}_0 > 1$, then the disease-free equilibrium of System (2.1) is unstable. Furthermore, there exists a constant $\eta > 0$, such that any solution $(W(t), E(t), I(t))$ of (2.1) with $I(0) > 0$ satisfies*

$$\limsup_{t \rightarrow \infty} I(t) \geq \eta.$$

Theorem 2 is proved in Appendix B.

According to Miller (1971), an endemic equilibrium of the system (2.1), if it exists, must satisfy the limiting system associated with (2.1), which is given by the following set of equations:

$$\begin{aligned} \frac{d}{dt}W &= \Lambda - B - \mu W + rI \\ E(t) &= \int_{-\infty}^t B(s)p(t-s)e^{-\mu(t-s)}ds \\ I(t) &= \int_{-\infty}^t a(t-s)B(s)ds \\ B(t) &= \beta cW(t) \frac{I(t)}{N(t)}. \end{aligned} \tag{2.4}$$

Let (W^*, E^*, I^*) be a constant solution of (2.4) with $I^* > 0$, and let $B^* = \beta cW^* \frac{I^*}{N^*}$. Then

$$\begin{aligned} I^* &= B^* \left(\int_{-\infty}^0 a(t-s)ds + \int_0^t a(t-s)ds \right) \\ &= B^* \left(\int_t^\infty a(\tau)d\tau + \int_0^t a(\tau)d\tau \right) \\ &= B^* D_I. \end{aligned} \tag{2.5}$$

Similarly we can get

$$E^* = B^* D_E. \tag{2.6}$$

Then by (2.5) we get

$$(2.7) \quad \frac{W^*}{N^*} = \frac{1}{\beta c D_I} = \frac{1}{\mathcal{R}_0}.$$

Using (2.6), (2.7) and $W^* + E^* + I^* = N^*$ we get

$$(2.8) \quad \begin{aligned} \frac{I^*}{N^*} &= \left(1 - \frac{1}{\mathcal{R}_0}\right) \frac{D_I}{D_I + D_E}, \\ \frac{E^*}{N^*} &= \left(1 - \frac{1}{\mathcal{R}_0}\right) \frac{D_E}{D_I + D_E}. \end{aligned}$$

Note that

$$(2.9) \quad \Lambda = B^* + \mu W^* - r I^*.$$

Dividing both sides of (2.9) by N^* and using (2.7), (2.8) we get

$$(2.10) \quad N^* = \frac{\Lambda \mathcal{R}_0}{\mu + (\mathcal{R}_0 - 1) \frac{1-rD_I}{D_I+D_E}}.$$

Note that $rD_I < (\mu + r + d)D_I = 1 - \mu D_E \leq 1$, hence $N^* > 0$ if $\mathcal{R}_0 > 1$. It is easy to see from (2.8) that only when $\mathcal{R}_0 > 1$ the unique endemic equilibrium exists and is given by

$$(2.11) \quad \begin{aligned} W^* &= \frac{1}{\mathcal{R}_0} N^*, \\ E^* &= \left(1 - \frac{1}{\mathcal{R}_0}\right) \frac{D_E}{D_I + D_E} N^*, \\ I^* &= \left(1 - \frac{1}{\mathcal{R}_0}\right) \frac{D_I}{D_I + D_E} N^*, \end{aligned}$$

where N^* is given by (2.10). The stability of the endemic equilibrium is given in the following result.

Theorem 3. *If $\mathcal{R}_0 > 1$, then the limiting system (2.4) has a unique endemic equilibrium which is locally asymptotically stable.*

We give the proof of Theorem 3 in Appendix C.

3. Discussion

In this paper we have constructed a TB model with a distributed delay to study the effect of variable periods of latency on the transmission dynamics of TB at the population level. These long and variable periods of latency were not considered in our previous paper

(see Castillo-Chavez and Feng 1996) as our emphasis there was on the study of resistant TB. The purpose of this paper is to look at the effects of variable (rather than exponentially distributed) periods of latency on the dynamics of TB.

We found that the qualitative dynamics of TB predicted by this model are no different from those given by our basic TB model with an exponentially distributed latency period (Castillo-Chavez and Feng 1996). The disease either dies out or remains endemic regardless of the shape of the incubation/latent period distribution. Blower et al. (1995) have developed a differential equation model with ‘two’ latent groups: one group involves those who will develop tuberculosis quickly after primary infection while a second group is formed of those who will develop disease slowly through endogenous reactivation. Since there is only one group of susceptible in their model, the ‘two-group’ effect is achieved by assuming that some fixed proportion of those who become infected (per unit of time) follows the fast route while the remaining proportion follows the slow route. The results of the model in this article show that this artificial division is not necessary and it plays no role in the qualitative dynamics. Furthermore, the division may cause confusion as it is not clear from their (Blower et al.) model how this fixed fraction could be selected in an epidemiologically or sociologically meaningful way. The fixed fraction model (referred to in Blower et. al. 1995) actually depends on factors that are not part of Blower et al.’s model and/or the model in this article (e.g. the age of the infected person). Age is a relevant factor, but it cannot *just* be assumed *a priori* that a fixed proportion of individuals in a particular age bracket develop active TB. Contact rates—conducive to TB transmission—are very likely to be age-dependent and the mixing between age-classes is nonlinear. Therefore, to study the dynamics of ‘fast’ versus ‘slow’ TB one must really use an age-structured model. The analysis of age-structured models, while complex, is not impossible (see Castillo-Chavez and Feng 1996a). Blower et al. (1995) compute \mathcal{R}_0 but study the dynamics of their model exclusively through simulations which turn out to be ‘typical’. Our analytical results have confirmed their limited simulations not only for the ‘slow/fast’ TB model but also for models where individuals progress towards active TB at ‘all’ possible rates. The fact that long and variable periods of ‘latency’ do not lead to complex dynamics has been worked out before. For example, Castillo-Chavez et al. (1989a, b, c) established that long and variable periods of infection for the transmission dynamics of HIV/AIDS have the same qualitative behavior as the dynamics of models with unrealistic exponentially distributed latent/infectious periods. However, factors such as exogenous infection and heterogeneous contact rates can indeed generate radically different dynamics than those given by the class of models discussed in this article. Exogenous reinfection is capable of sustaining TB even when the basic reproductive number $\mathcal{R}_0 < 1$ (see Castillo-Chavez and Feng 1996b). Computation of the reproductive number in this article helps understand the role that key epidemiological parameters play in the maintenance of TB—including the role of the

parameters associated with an arbitrary distribution that models long and variable periods of latency.

To summarize our perspective: a person infected with TB may develop active TB in a variety of ways. One possibility is that a person may develop active TB as a result of an endogenous infection—the subject of this article. In this case, there is no impact on the qualitative dynamics of the transmission dynamics of TB. A second possibility is that such a person may develop active TB as a consequence of exogenous reinfection (i.e., acquiring a new infection from another infectious individual; Smith 1993). Our results show that exogenous reinfection can have a drastic effect on the qualitative dynamics of TB (see Castillo-Chavez, Feng and Capurro 1996). The incorporation of exogenous reinfection into the basic TB model of Section 1 allows for the possibility of a subcritical bifurcation. Thus, a “backwards” bifurcation of an endemic equilibrium may occur at the critical value of the reproductive number $\mathcal{R}_0 = 1$ and hence, our system can have multiple endemic equilibria for $\mathcal{R}_0 < 1$. This type of behavior has been observed in recent epidemiological models in the context of sexually-transmitted diseases (see Haderler and Castillo-Chavez 1995). Mixing plays a key role in TB transmission. We are particularly interested in looking at the effects of age-dependent contact rates on TB dynamics as well as contact rates that are dependent on the place of activity (the role of household contact rates versus the role of contact rates experienced by users of public transportation). The formulation of models with age-dependent contact rates (or other heterogeneous contact rates) even under the assumption of proportionate mixing, leads to hyperbolic systems of partial differential equations that are difficult to analyze (but see Castillo-Chavez and Feng 1996a). Nevertheless, preliminary results are possible and we plan to use them to study not only the role of endogenous infection but also the effectiveness of TB vaccines (such as the BCG vaccine) on the dynamics of TB within age-structured populations.

Acknowledgments This research was partially supported by NSF grant DEB-925370 (Presidential Faculty Fellowship Award) to Carlos Castillo-Chavez and by the U.S. Army Research Office through the Mathematical Science Institute of Cornell University (contract DAAL03-91-0027).

Appendix A: The global stability of the disease-free equilibrium

For a bounded real-valued function f on $[0, \infty)$ we define

$$f_\infty = \liminf_{t \rightarrow \infty} f(t), \quad f^\infty = \limsup_{t \rightarrow \infty} f(t).$$

Lemma 1 (*Thieme 1993*) *Let $f : [0, \infty) \rightarrow \mathbf{R}$ be bounded and twice differentiable with bounded second derivative. Let $t_n \rightarrow \infty$ and $f(t_n)$ converge to f^∞ or f_∞ for $n \rightarrow \infty$. Then*

$$f'(t_n) \rightarrow 0, \quad n \rightarrow \infty.$$

The proof of Theorem 1:

Let $\mathcal{R}_0 < 1$. Differentiating the E and I equations in (2.1) and using the fact that $E_0(t), I_0(t)$ have compact supports, we get

$$(A1) \quad \frac{d}{dt}E = B + \int_0^t B(s)\dot{p}(t-s)e^{-\mu(t-s)}ds - \mu E,$$

and

$$(A2) \quad \frac{d}{dt}I = -(\mu + r + d)I - \int_0^t B(s)\dot{p}(t-s)e^{-\mu(t-s)}ds - (\mu + r + d)I_0e^{-(\mu+r+d)t}$$

for large t . Then

$$(A3) \quad \frac{d}{dt}N = \Lambda - \mu N - dI - (\mu + r + d)I_0e^{-(\mu+r+d)t}.$$

Noticing that

$$\Lambda - (\mu + d)N - (\mu + r + d)I_0e^{-(\mu+r+d)t} \leq \frac{d}{dt}N \leq \Lambda - \mu N,$$

and using Lemma 1 we get

$$\frac{\Lambda}{\mu + d} \leq N_\infty \leq N^\infty \leq \frac{\Lambda}{\mu}.$$

Hence we can assume, without loss of generality, that $\Lambda/\mu + d \leq N(t) \leq (\Lambda/\mu)$ for $t \geq 0$.

Claim that $I^\infty = 0$.

Suppose $I^\infty > 0$. Note that $-\dot{p}(t) \geq 0$ and

$$(A4) \quad \begin{aligned} 0 &\leq \int_0^{t_n} -\dot{p}(t_n - s)e^{-\mu(t_n - s)}ds \\ &= \int_0^{t_n} -\dot{p}(\tau)e^{-\mu\tau}d\tau \\ &\rightarrow \int_0^\infty -\dot{p}(\tau)e^{-\mu\tau}d\tau \\ &= 1 - \mu D_E, \quad t \rightarrow \infty. \end{aligned}$$

By (A4), Lemma 1 and the $\frac{d}{dt}I$ equation (A2), we can choose a sequence $t_n \rightarrow \infty$ such that

$$\frac{d}{dt}I(t_n) \rightarrow 0, \quad \text{as } I(t_n) \rightarrow I^\infty,$$

and

$$(A5) \quad \begin{aligned} 0 &\leq -(\mu + r + d)I^\infty + \beta c \left(\frac{N - E - I^\infty}{N} \right)^\infty I^\infty \int_0^\infty -\dot{p}(\tau) e^{-\mu(\tau)} d\tau \\ &\leq -(\mu + r + d)I^\infty + \beta c \left(1 - \frac{\mu}{\Lambda} I^\infty \right) I^\infty (1 - \mu D_E). \end{aligned}$$

Note that $I^\infty > 0$ and

$$(A6) \quad \frac{1 - \mu D_E}{\mu + r + d} = D_I = \frac{\mathcal{R}_0}{\beta c}.$$

Then (A5) gives

$$I^\infty \leq \frac{\Lambda}{\mu} \left(1 - \frac{1}{\mathcal{R}_0} \right),$$

indicating that $I^\infty \leq 0$ since $\mathcal{R}_0 < 1$. This contradicts $I^\infty > 0$.

Note that for any positive solution of (2.1) $I_\infty \geq 0$. It follows that $I_\infty = I^\infty = 0$, hence

$$(A7) \quad \lim_{t \rightarrow \infty} I(t) = 0.$$

Note that

$$B^\infty \leq \beta c W^\infty \frac{I^\infty}{N_\infty} = 0.$$

By Lemma 1 and the $\frac{d}{dt}E$ equation (A1), we can choose $s_n \rightarrow \infty$ such that $\frac{d}{dt}E(s_n) \rightarrow 0$, $E(s_n) \rightarrow E^\infty$, and $0 \leq -\mu E^\infty$. This implies that $E^\infty = 0$, i.e.,

$$(A8) \quad \lim_{t \rightarrow \infty} E(t) \rightarrow 0.$$

Similarly, using Lemma 1 and the $\frac{d}{dt}W$ equation in (2.1), we have $0 \geq \Lambda - \mu W_\infty$. Hence $W_\infty \geq \Lambda/\mu$. But $W^\infty \leq \Lambda/\mu$, hence $W_\infty = W^\infty = \Lambda/\mu$, i.e.,

$$(A9) \quad \lim_{t \rightarrow \infty} W(t) = \frac{\Lambda}{\mu}.$$

>From (A7), (A8), and (A9) we have

$$\lim(W(t), E(t), I(t)) \rightarrow \left(\frac{\Lambda}{\mu}, 0, 0 \right), \quad t \rightarrow \infty$$

for all positive solution of (2.1).

Appendix B: Stability and instability for the system (2.1)

Lemma 2. If $\mathcal{R}_0 > 1$, then any solution $(W(t), E(t), I(t))$ of (2.1) with $I(0) > 0$ satisfies

$$\limsup_{t \rightarrow \infty} I(t) > 0.$$

Proof: Since $I_0(t)$ has compact support, we can replace the I equation in (1.5) by

$$(B0) \quad I(t) = I_0 e^{-(\mu+r+d)t} + \int_0^t a(t-s)B(s)ds.$$

Suppose that the conclusion of the Lemma is not true. Then $I^\infty = 0$, or $\lim_{t \rightarrow \infty} I(t) = 0$. This also implies that (see the proof of Theorem 1) $\lim_{t \rightarrow \infty} E(t) = 0$. It follows that $\lim_{t \rightarrow \infty} W(t)/N(t) = 1$. Hence there is a sequence $\{k_n\} > 0$ such that $k_n \rightarrow \infty$ as $n \rightarrow \infty$, and

$$(B1) \quad \frac{W(t)}{N(t)} > 1 - \frac{1}{n}, \quad \text{for all } t \geq k_n.$$

Note by (A2), that $\frac{d}{dt}I(t) \rightarrow 0$ as $t \rightarrow \infty$. Whenever $I(t)$ gets close to 0 for large t it will stay close to 0 for a long time. Also noticing that $I(0) > 0$ and $I^\infty = 0$, we can find sequences s_n, t_n such that $t_n - s_n \rightarrow \infty$, $s_n \rightarrow \infty$ and

$$(B2) \quad I(t) \geq I(t_n), \quad t \in (s_n, t_n).$$

Then by (B0), (B1), and (B2), after choosing a subsequence, we get

$$(B3) \quad \begin{aligned} I(t_n) &= I_0 e^{-(\mu+r+d)t_n} + \int_0^{t_n} a(t_n-s)\beta c W(s) \frac{I(s)}{N(s)} ds \\ &> \beta c \left(1 - \frac{1}{n}\right) I(t_n) \int_{s_n}^{t_n} a(t_n-s) ds. \end{aligned}$$

Note that $I(t_n) > 0$ for all n and

$$(B4) \quad \int_{s_n}^{t_n} a(t_n-s) ds = \int_0^{t_n-s_n} a(\tau) d\tau \rightarrow D_I, \quad n \rightarrow \infty.$$

Then by (B3) and (B4), dividing both sides of (B3) by $I(t_n)$ and taking $n \rightarrow \infty$, we get

$$1 \geq \beta c D_I = \mathcal{R}_0.$$

But $\mathcal{R}_0 > 1$, a contradiction.

The proof of Theorem 2:

Using Lemma 1, by (A4) and the $\frac{d}{dt}E$ equation (A1) we have

$$\begin{aligned} 0 &\leq \beta c(W \frac{I}{N})^\infty + \beta c(W \frac{I}{N})_\infty (\mu D_E - 1) - \mu E^\infty \\ &\leq \beta c(W \frac{I}{N})^\infty (1 + \mu D_E) - \mu E^\infty \\ &\leq \beta c I^\infty (1 + \mu D_E) - \mu E^\infty, \end{aligned}$$

or

$$(B5) \quad E^\infty \leq \frac{\beta c}{\mu} (1 + \mu D_E) I^\infty.$$

Similarly by the $\frac{d}{dt}I$ equation in (A2) and Lemma 1 we have

$$\begin{aligned} (B6) \quad 0 &\geq \beta c(\frac{W}{N})_\infty I^\infty (1 - \mu D_E) - (\mu + r + d) I^\infty \\ &\geq \beta c[1 - (\frac{E + I}{N})^\infty] (1 - \mu D_E) I^\infty - (\mu + r + d) I^\infty. \end{aligned}$$

Since $I^\infty > 0$ by Lemma 2, (B6) yields

$$(B7) \quad (\frac{E + I}{N})^\infty \geq 1 - \frac{1}{\mathcal{R}_0}.$$

On the other hand, from (B5) we can get

$$(B8) \quad (\frac{E + I}{N})^\infty \leq (1 + \frac{\beta c}{\mu} (1 + \mu D_E)) \frac{I^\infty}{N_\infty}.$$

Let

$$\eta = \frac{(1 - \frac{1}{\mathcal{R}_0}) \frac{\Lambda}{\mu + d}}{1 + \frac{\beta c}{\mu} (1 + \mu D_E)},$$

then $\eta > 0$ since $\mathcal{R}_0 > 1$. By (B7) and (B8) we get

$$I^\infty \geq \eta.$$

Appendix C: Asymptotic stability of the endemic equilibrium

The proof of this result reduces to the study of the local stability of the trivial equilibrium ($X = 0$) for a Volterra integral equation of the type

$$(C1) \quad X(t) = F(t) + \int_0^t A(t-s) G(X(s)) ds,$$

where $X \in \mathbf{R}^n$, $G(0) = 0$, $G \in C^1(\mathbf{R}^n \rightarrow \mathbf{R}^n)$, $F \in C([0, \infty) \rightarrow \mathbf{R}^n)$, A is an $n \times n$ matrix such that $A(t) \in L^1[0, t]$ for each $t > 0$. \mathbf{R}^n denotes real n -space with a norm $|X|$, and $|A|$ denotes the corresponding matrix norm.

Theorem (Miller 1968; Theorem 4). Assume that the following conditions hold:

- (i) the Jacobian matrix $DG(0)$ is nonsingular,
 - (ii) $\det(I_n - \int_0^\infty e^{-\lambda\tau} A(\tau) DG(0) d\tau) \neq 0$, for all λ with $\Re \lambda \geq 0$, where I_n denotes the $n \times n$ identity matrix, and
 - (iii) there is a sufficiently small $\epsilon_0 > 0$ such that $\{\sup |F(t)|; 0 \leq t < \infty\} \leq \epsilon_0$ and $F(t) \rightarrow 0$ as $t \rightarrow \infty$.
- Then $X(t) \rightarrow 0$ as $t \rightarrow \infty$.

Proof of Theorem 3:

First we rewrite the W equation in (2.4) as

$$(C2) \quad W(t) = \frac{\Lambda}{\mu} + (W(0) - \frac{\Lambda}{\mu})e^{-\mu t} + \int_0^t (rI(s) - B(s))e^{-\mu(t-s)} ds.$$

Noticing that

$$(C3) \quad B(t) = \Lambda + rI(t) - e^{-\mu t} \frac{d}{dt} (W(t)e^{\mu t}),$$

we can then write the E equation in (2.4) as

$$(C4) \quad \begin{aligned} E(t) &= \int_0^t B(s)p(t-s)e^{-\mu(t-s)} ds \\ &= \int_0^t [\Lambda + rI(t) - e^{-\mu t} \frac{d}{dt} (W(t)e^{\mu t})] p(t-s)e^{-\mu(t-s)} ds \\ &= \Lambda \int_0^t p(\tau)e^{-\mu\tau} d\tau + r \int_0^t I(s)p(t-s)e^{-\mu(t-s)} ds \\ &\quad - \int_0^t \frac{d}{dt} (W(s)e^{\mu s}) p(t-s)e^{-\mu t} ds \\ &= \Lambda \int_0^t p(\tau)e^{-\mu\tau} d\tau + r \int_0^t I(s)p(t-s)e^{-\mu(t-s)} ds \\ &\quad - W(t) + W(0)p(t)e^{-\mu t} - \int_0^t W(s)\dot{p}(t-s)e^{-\mu(t-s)} ds. \end{aligned}$$

We next transform System (2.4) to the origin by letting

$$\hat{W} = W - W^*, \quad \hat{E} = E - E^*, \quad \hat{I} = I - I^*.$$

Let

$$(C5) \quad \hat{B}(t) = \beta c W(t) \frac{I(t)}{N(t)} = \beta c (\hat{W}(t) + W^*) \frac{\hat{I}(t) + I^*}{\hat{N}(t) + N^*},$$

where

$$N^* = W^* + E^* + I^*, \quad \hat{N}(t) = \hat{W}(t) + \hat{E}(t) + \hat{I}(t).$$

Then noticing that

$$(C6) \quad \int_0^t B^* e^{-\mu(t-s)} ds = \left(\frac{\Lambda}{\mu} - W^* + \frac{rI^*}{\mu} \right) (1 - e^{-\mu t}),$$

and by (C2) – (C6), we have

$$(C7) \quad \begin{aligned} \hat{W}(t) &= \hat{W}(0)e^{-\mu t} + r \int_0^t \hat{I}(s)e^{-\mu(t-s)} ds - \int_0^t (\hat{B}(s) - B^*)e^{-\mu(t-s)} ds, \\ \hat{E}(t) &= \hat{W}(0)(p(t) - 1)e^{-\mu t} + \int_{-\infty}^0 (\hat{B}(s) - B^*)p(t-s)e^{-\mu(t-s)} ds \\ &\quad + r \int_0^t \hat{I}(s)(p(t-s) - 1)e^{-\mu(t-s)} ds + \int_0^t (\hat{B}(s) - B^*)e^{-\mu(t-s)} ds \\ &\quad - \int_0^t \hat{W}(s)\dot{p}(t-s)e^{-\mu(t-s)} ds, \\ \hat{I}(t) &= \int_{-\infty}^0 (B(s) - B^*)a(t-s)ds + \int_0^t (B(s) - B^*)a(t-s)ds. \end{aligned}$$

Then System (C7) is in the form (C1) with

$$(C8) \quad F(t) = \begin{pmatrix} \hat{W}(0)e^{-\mu t} \\ \hat{W}(0)(p(t) - 1)e^{-\mu t} + \int_{-\infty}^0 (\hat{B}(s) - B^*)e^{-\mu(t-s)} ds \\ \int_{-\infty}^0 (\hat{B}(s) - B^*)a(t-s)ds \end{pmatrix},$$

$$(C9) \quad A(\tau) = \begin{pmatrix} 0 & -e^{-\mu\tau} & re^{-\mu\tau} \\ -\dot{p}(\tau)e^{-\mu\tau} & e^{-\mu\tau} & r(p(\tau) - 1)e^{-\mu\tau} \\ 0 & a(\tau) & 0 \end{pmatrix},$$

$$(C10) \quad G(X) = \begin{pmatrix} \hat{W} \\ \hat{B} - B^* \\ \hat{I} \end{pmatrix},$$

$$(C11) \quad X = \begin{pmatrix} \hat{W} \\ \hat{E} \\ \hat{I} \end{pmatrix}.$$

It remains to show that the conditions specified in Miller's theorem are satisfied. To simplify expressions, let

$$x = \frac{W^*}{N^*}, \quad y = \frac{E^*}{N^*}, \quad z = \frac{I^*}{N^*}.$$

Note that

$$(C12) \quad DG(0) = \begin{pmatrix} 1 & 0 & 0 \\ \beta cz(y+z) & -\beta cxz & \beta cx(x+y) \\ 0 & 0 & 1 \end{pmatrix}.$$

Then $\det DG(0) = -\beta cxz \neq 0$ since $x > 0, z > 0$ when $\mathcal{R}_0 > 1$. The condition (i) is satisfied.

Next we check the condition (ii). Note by (C9) and (C12) that

$$A(\tau)DG(0) = \begin{pmatrix} -e^{-\mu\tau}m_3 & e^{-\mu\tau}m_2 & e^{-\mu\tau}(r-m_1) \\ e^{-\mu\tau}[m_3-\dot{p}(\tau)] & -e^{-\mu\tau}m_2 & e^{-\mu\tau}[m_1+r(p(\tau)-1)] \\ a(\tau)m_3 & -a(\tau)m_2 & a(\tau)m_1 \end{pmatrix},$$

where

$$(C13) \quad m_1 = \beta cx(x+y), \quad m_2 = \beta cxz, \quad m_3 = \beta cz(y+z).$$

Then

$$\begin{aligned} H(\lambda) &= \det \left(I_n - \int_0^\infty e^{-\lambda\tau} A(\tau) DG(0) d\tau \right) \\ &= \begin{pmatrix} 1 + \frac{m_3}{\mu+\lambda} & -\frac{m_2}{\mu+\lambda} & \frac{m_1-r}{\mu+\lambda} \\ \int_0^\infty \dot{p}(\tau) e^{-(\mu+\lambda)\tau} d\tau - \frac{m_3}{\mu+\lambda} & 1 + \frac{m_2}{\mu+\lambda} & \frac{r-m_1}{\mu+\lambda} - r \int_0^\infty p(\tau) e^{-(\mu+\lambda)\tau} d\tau \\ -m_3 \int_0^\infty a(\tau) e^{-\lambda\tau} d\tau & m_2 \int_0^\infty a(\tau) e^{-\lambda\tau} d\tau & 1 - m_1 \int_0^\infty a(\tau) e^{-\lambda\tau} d\tau \end{pmatrix}. \end{aligned}$$

After canceling terms we get

$$\begin{aligned} (C14) \quad H(\lambda) &= 1 + \frac{m_3}{\mu+\lambda} + \frac{m_2}{\mu+\lambda} \\ &\quad - \left(m_1 + \frac{rm_3}{\mu+\lambda} \right) \int_0^\infty a(\tau) e^{-\lambda\tau} d\tau \\ &\quad + \frac{m_2}{\mu+\lambda} \int_0^\infty \dot{p}(\tau) e^{-(\mu+\lambda)\tau} d\tau. \end{aligned}$$

It is easier to estimate $|H(\lambda)|$ if we express $\int_0^\infty \dot{p}(\tau) e^{-(\mu+\lambda)\tau} d\tau$ in terms of $\int_0^\infty a(\tau) e^{-\lambda\tau} d\tau$. Using the definition of $a(t)$ (see 1.3) we have

$$(C15) \quad \int_0^\infty \dot{p}(\tau) e^{-(\mu+\lambda)\tau} d\tau = -(\mu+r+d+\lambda) \int_0^\infty a(\tau) e^{-\lambda\tau} d\tau.$$

Then (C14) and (C15) yield

$$\begin{aligned} (C16) \quad |H(\lambda)| &\geq \left| 1 + \frac{m_3}{\mu+\lambda} + \frac{m_2}{\mu+\lambda} \right| \\ &\quad - \left| \left(m_1 + m_2 + \frac{rm_3}{\mu+\lambda} + \frac{m_2(r+d)}{\mu+\lambda} \right) \int_0^\infty a(\tau) e^{-\lambda\tau} d\tau \right|. \end{aligned}$$

Since $\Re\lambda \geq 0$, we have $\int_0^\infty |a(\tau)e^{-\lambda\tau}|d\tau \leq D_I$. Note that

$$\begin{aligned}
(C17) \quad x &= \frac{W^*}{N^*} = \frac{1}{\mathcal{R}_0}, \\
\beta c D_I &= \mathcal{R}_0, \\
(m_1 + m_2) D_I &= \beta c x (x + y + z) D_I = 1, \\
r D_I &\leq (r + d) D_I < (\mu + r + d) D_I = 1 - D_E < 1.
\end{aligned}$$

Then by (C15) – (C17) we can show that

$$\begin{aligned}
|H(\lambda)| &\geq \left| 1 + \frac{m_3}{\mu + \lambda} + \frac{m_2}{\mu + \lambda} \right| \\
&\quad - \left| (m_1 + m_2) D_I + \frac{m_3}{\mu + \lambda} r D_I + \frac{m_2}{\mu + \lambda} (r + d) D_I \right| \\
&> 0,
\end{aligned}$$

whenever $\Re\lambda \geq 0$.

Furthermore, clearly for any $\epsilon_0 > 0$, there is a $\delta_0 > 0$ such that $\{\sup |F(t)| : 0 \leq t < \infty\} \leq \epsilon_0$ and $F(t) \rightarrow 0$ as $t \rightarrow \infty$, for any $|\hat{W}(\tau)| \leq \delta_0$, $|\hat{E}(\tau)| \leq \delta_0$, $|\hat{I}(\tau)| \leq \delta_0$, and $-\infty \leq \tau \leq 0$.

References

- Alland, D., Kalkut, G.E., Moss, A.R., McAdam, R.A., Hahn, J.A., Bosworth, W., Drucker, E., Bloom, B.R.: Transmission of tuberculosis in New York City: An analysis by DNA fingerprinting and conventional epidemiological methods. *New England Journal of Medicine*. **330**, 1710-1716. (1994)
- Anderson, R.M.: *Population dynamics of infectious diseases*. London, New York: Chapman and Hall (1982)
- Anderson, R.M., May, R.M.: *Population biology of infectious diseases*. Berlin, Heidelberg, New York: Springer-Verlag (1982)
- Anderson, R.M., May, R.M.: *Infectious Diseases of Humans*. Oxford New York Tokyo: Oxford University Press (1991).
- Ayvazain, L.F.: History of tuberculosis. Reichman, L.B.; Hershfield, E.S. (eds.) *Tuberculosis: A Comprehensive International Approach*. pp.1-20 New York 1993.
- Blower, S.M., McLean A. R., Porco, T. C., Small, P. M., Hopwell, P.C., Sanchez, M. A., Moss, A. R.: The intrinsic transmission dynamics of tuberculosis epidemics. *Nature Medicine*. **1**, 815-821 (1995)
- Boucot, K. R., Dillon, E. S., Cooper, D. A. and Meir, P.: Tuberculosis among diabetics: The Philadelphia survey. *Am. Rev. Tuberc.* **65** (suppl.), 1-50 (1952).

- Brown, D.H., Miles, B.A., Zwillig, B.S.: Growth of Mycobacterium tuberculosis in BCG-Resistant and - Susceptible Mice: Establishment of Latency and Reactivation. *Infection and Immunity*. **63**, 2243-2247. (1995)
- Castillo-Chavez, C., Cooke, K., Huang, W., Levin, S.A.: Results on the Dynamics for Models for the sexual Transmission of the Human Immunodeficiency Virus. *Appl. Math. Lett.* **2**, 327-331. (1989a)
- Castillo-Chavez, C., Cooke, K., Huang, W., Levin, S.A.: On the Role of Long Periods of Infectiousness in Models of the Transmission Dynamics of the Acquired Immunodeficiency Syndrome (AIDS). In : Castillo-Chavez, C., Levin, S.A., Shoemaker, C.A. (eds.): *Mathematical Approaches to Problems in Resources Management and Epidemiology*. Lectures Notes in Biomathematics, **81**. Springer-Verlag. (1989b).
- Castillo-Chavez, C., Cooke, K., Huang, W., Levin, S.A.: On the Role of Long Periods of Infectiousness in Models of the Transmission Dynamics of the Acquired Immunodeficiency Syndrome (AIDS). Part 1. *J. Math. Biol.* **27**, 373-398. (1989c)
- Castillo-Chavez, C., Feng, Z.: To treat or not to treat: the case of tuberculosis. To appear. *J. Math. Biol.* (1996)
- Castillo-Chavez, C., Feng, Z.: Optimal vaccination strategies for TB in age-structure populations. Submitted, *J. Math. Biol.* (1996a)
- Castillo-Chavez, C., Feng, Z.: Mathematical Models for the Disease Dynamics of Tuberculosis. Submitted. *Proceedings of the Fourth International Conference on Mathematical Population Dynamics*. (1996b)
- Castillo-Chavez, C., Feng, Z. and Capurro F. C.: A TB Model with Exogenous Reinfection. Manuscript. (1996)
- Castillo-Chavez, C., Hethcote, H.W., Andreason, V. Levin, S.A., Liu, W.: Cross-immunity in the dynamics of homogeneous and heterogeneous populations. In: Gross, L., Hallam, T.G., Levin, S.A. (eds.) *Mathematical ecology*. Proceedings, Autumn Course Research Seminars, Trieste 1986, pp.303-316. Singapore: World Scientific Publ. Co. (1988).
- Castillo-Chavez, C., Hethcote, H.W., Andreason, V. Levin, S.A., Liu, W.: Epidemiological models with age structure, proportionate mixing, and cross-immunity. *J. Math. Biol.* **27**, 233-258 (1989)
- Chan, J., Kaufman, S. H. E.: Immune mechanics of protection. In: Bloom, R. (Ed). *Tuberculosis: Pathogenesis, Protection and Control*. AMS, Washington, 1994
- Comstock, G. W., Edwards P.Q.: The competing risks of tuberculosis and hepatitis for adult tuberculin reactors. *Am. Rev. Respir. Dis.* **87** (suppl), 1-88 (1975)
- Comstock, G. W., Livesay, V.T., Woolpert, S. F.: The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am. J. Epidemiol.* **99**, 131-138 (1974)
- Dietz, K.: Epidemiologic interference of virus populations. *J. Math. Biol.* **8**, 291-300

- (1979)
- Dietz, K., Schenzle, D.: Proportionate mixing models for age-dependent infection transmission. *J.Math. Biol.* **22**, 117-120 (1985)
- Dunlap, N.E., Briles, D.E. Immunology of tuberculosis. *Medical Clinics of North America.* **77**, 1235-1251 (1993)
- Dutt, A.K., Stead, W.W. Tuberculosis in the elderly. *Medical Clinics of North America.* **77**, 1353-1368. (1993)
- Feng, Z., Thieme, R.H.: Multi-annual outbreaks of childhood disease revisited: the impact of isolation. *Math. Biosci.* **128**, 93-130 (1995)
- Feng, Z. (thesis): A mathematical model for the dynamics of childhood disease under the impact of isolation. Arizona State University (1994)
- Goodman, R. M. , Motulsky, A. G.: *Genetic Diseases among Askenazi Jews* page 301. Raven Press, Inc. New York (1979)
- Hadeler, K.P., Castillo-Chavez, C.: A core group model for disease transmission. *Math. Biosci.* **128**, 41-55 (1995)
- Henri, J. , Bennett, O.H.: Tuberculosis and NIDDM: New dimensions to an old problem. *Abstracts from the 12th Congress of IDF.* Sept 23-28, Madrid, Spain. Elsevier Publishers, Amsterdam, p. S234. (1985)
- Hethcote, H.W.: Qualitative analysis for communicable disease models. *Math. Biosci.* **28**, 335-356 (1976)
- Hethcote, H.W., Stech, H.W., van den Driessche, P. Periodicity and stability in epidemic models: a survey. In: Busenberg, S., Cooke, K.L. (eds.) *Differential equations and applications in ecology, epidemics, and population problems.* pp. 65-82. New York: Academic Press 1981
- Hethcote, H.W., Van Ark, J.W.: Epidemiological models for heterogenous populations: proportionate mixing, parameter estimation, and immunization programs. *Math. Biosci.* **84**, 85-118 (1987)
- Hopewell, P.C.: Overview of clinical tuberculosis. Bloom B.R. (ed.) *Tuberculosis: Pathogenesis, Protection, and Control.* pp. 25-46 (1994)
- Kent, J.H.: The epidemiology of multi-drug resistant tuberculosis in the United States. *Medical clinics of North America.* **77**, 1-6 (1991)
- Kochi, A.: The Global Tuberculosis Situation and the New Control Strategy of the World Health Organization. *Tubercle* **72**, 1-6 (1991)
- Medical Research Council: BCG and vole bacillus in the prevention of tuberculosis in adolescence and early adult life. *Bull. Wld. Hlth. Org.* **46** 3785 (1972)
- Miller, Bess.: Preventive Therapy for Tuberculosis. *Medical clinics of North America.* **77**, 1263-1275 (1993)

- Miller, R.K.: On the linearization of Volterra integral equations. *J. Math. Anal. Appl.* **23** 198-208 (1968)
- Miller, R.K.: *Nonlinear Volterra integral equations*. W.A. Benjamin Inc. 1971.
- Miller, R.A, Lanza, L. A., Kline, J. N., Geist, L.J.: *Mycobacterium tuberculosis* in lung transplant recipients. *American Journal of Respiratory and Critical Care Medicine*. **152**, 374-376. (1995)
- Opshal, R., Riddervold, H.O., Aas, T.W.: Pulmonary tuberculosis in mitral stenosis and diabetes mellitus. *Acta Med. Scand.* **40**, 290-296 (1961)
- Oscarrson, P.N., Silwer, H.: Incidence of pulmonary tuberculosis among diabetics. *Acta Med. Scand.* **161** (suppl.), 23-48 (1958)
- Reichman, L.B.; Hershfield, E.S.: *Tuberculosis: A Comprehensive International Approach*. New York 1993.
- Schenzle, D.: An age-structured model of pre- and post-vaccination measles transmission. *IMA J. Math. Appl. Med. Biol.* **1**, 169-191 (1984)
- Selwyn, P. A. Hartel, D., Lewis, V. A., Schoenbaum, E. E., Vermun, S.H., Klein, R. S., Walker, A.T., Friedland, G.H.: A Prospective Study of the Risk of Tuberculosis Among Intravenous Drug Users with Human Immunodeficiency Virus Infection. *N Engl J Med.* **320**, 545-550. (1989)
- Sifford, M , Bates JH.: Host determinants of susceptibility to Mycobacterium tuberculosis. *Semin Respir Infect.* **6**, 44-50. (1991)
- Skamene, E.: Genetic control of resistance to mycobacterial infection. *Curr. Top. Microbiol. Immunol.* **124**, 49-66 (1986)
- Smith, P.G., Moss, A.R.: Epidemiology of tuberculosis. Bloom B.R. (ed.) *Tuberculosis: Pathogenesis, Protection, and Control* pp. 47-59 (1994)
- Snider, D.E., Raviglione, M., Kochi, A.: Global burden of tuberculosis. Bloom B.R. (ed.) *Tuberculosis: Pathogenesis, Protection, and Control* pp. 47-59 (1994)
- Styblo, K.: Selected Papers: Epidemiology of Tuberculosis. *Royal Netherlands Tuberculosis Association.* **24**, 55-62 (1991)
- Thieme, R.H.: Persistence under relaxed point-dissipativity (with applications to an endemic model). *SIAM J. Math. Anal.* **24**, 407-435 (1993)
- Warwick, M.T.: Pulmonary tuberculosis and diabetes mellitus. *Q. J. Med.* **26**, 30-34 (1957)